IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of Koral Embil and Sergio Nacht	:	Group Art Unit 1615
Serial No.: 10/761,390	:	Examiner Channavajjala
For: Topical Pharmaceutical and/or Cosmetic Dispense Systems	:	
Filed: January 22, 2002	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration of Martin Katz, Sc.D. Under 37 C.F.R. § 1.132

I, Martin Katz, being duly sworn depose and say:

1. I have prepared this declaration so that it may be considered by the US Patent and Trademark Office in connection with Patent Application Serial No. 10/761,390 (the "Embil/Nacht Appln").

2. I received a Bachelor of Science degree in Pharmacy from St. Johns University in Queens, NY, a Masters of Arts degree in General Chemistry and a Masters of Science degree in Pharmaceutical Sciences, both from Columbia University in New York, NY, and a Doctor of Sciences (Sc.D.) in Pharmacology from the University of Sciences in Philadelphia, PA. I am a Registered Pharmacist and Fellow of both the Academy of Pharmaceutical Sciences and the Society of Cosmetic Chemists.

3. From 1953 – 1955, including while completing my doctorate, I was a Group Leader at Pfizer. Thereafter, from 1955 – 1960, I was a Group Leader at Revlon. For the next 25 years, from 1960 – 1985, I worked at Syntex Research (Palo Alto, CA). Throughout my employment at Syntex, including in my capacity as Senior Vice President of Pharmaceutical Research, I helped develop well-known prescription and OTC products, including the oral contraceptive Norinyl®, the non-steroidal anti-inflammatory

naproxen (Aleve®), and topical corticosteroids, Synalar® and Lidex®. My work with colleagues at Syntex is described in over 40 publications and patents.

4. After retiring from Syntex, I became Senior Vice President, Research and Development at Advanced Polymer Systems, where I was a co-inventor of polymeric delivery systems, including the Microsponge. The latter system has been used in topical products to effectively deliver active ingredients with reduced irritancy. Among these are Retin-A (J&J) and 5-fluorouracil (Carac® by Dermik).

5. In preparing this Declaration, I have reviewed the following documents:

(i) the Embil/Nacht Appln;

(ii) the Non-Final Office Action dated April 9, 2007;

(iii) the Response to Non-Final Office dated October 9, 2007;

(iv) the Declaration of Robert Y. Lochhead submitted in connection with the October 9, 2007 Response to Non-Final Office Action; and

(v) the Non-Final Office Action dated December 27, 2007, including the four prior art references which form the basis for rejecting the claims of the Embil/Nacht Appln as obvious under 35 U.S.C. § 103(a)

(a) International Patent Application WO 9315726 ("W026");

(b) European Patent Application EP 306236 ("EP");

(c) US Patent No. 5,879,716 ("Katz");

(d) the article by Wester *et. al.* in *Journal of the American Academy of Dermatology*, Vol. 24, No. 6, pp. 720-726, (May, 1991) ("Wester");

6. I am a co-inventor on the compositions described in two of the four cited prior art references – Katz and EP.

7. A person having ordinary skill in the art of formulating cosmetic and pharmaceutical topical products would read and understand the claims of the

Embil/Nacht Appln – both as originally-filed and published in US Patent Application Publication 2004/0157766 and later amended in the Response to Non-Final dated October 9, 2007 – in the following manner: The topical product claimed by Drs. Embil and Nacht is comprised of two formulations, both of which contain aqueous carrier bases that have substantially the same lipophilicity. The latter requirement – having substantially the same lipophilicity – is defined in Paragraph [0068] of the Embil/Nacht Appln in terms of partition coefficient. More specifically, Drs. Embil and Nacht discuss the importance of having two compositions in which the partition coefficient of the carriers of the two compositions and the partition coefficient of an active ingredient entrapped within a polymeric delivery system (e.g., Microsponge) vary by no more than 10%, advantageously by no more than 5% and preferably by no more than 2.5%.

8. It is my understanding that the Embil/Nacht Appln has been amended in the Response to Non-Final Office Action filed together with this Declaration to more particularly claim compositions in which the partition coefficient of the two water-based carrier compositions (at least one of which contains an active ingredient entrapped within a polymeric delivery system) and the partition coefficient of the active ingredient entrapped within the polymeric delivery system (e.g., Microsponge) vary by no more than 10% (New Claim 33), by no more than 5% (New Claim 34) and by no more than 2.5% (New Claim 35).

9. WO26 does not teach or suggest matching lipophilicity or partition coefficient. Indeed, there are only nine (9) non-specific references to the carrier in WO26. At most, these references teach a "pharmaceutically acceptable fluid carrier including a gelling agent at a concentration of from 0.1% by weight to 5% by weight" (see WO26 Claim 26) which is aqueous (see WO26 Claim 30).

10. Page 3 of the December 2007 Non-Final Office Action makes a conclusory

statement, without explanation, that "the compositions of two components [of the combination benzoyl peroxide/clindamycin product taught in WO26] ... do not appear to vary in their hydrophilicity or lipophilicity." This statement is contrary to the scientific explanation offered in Paragraphs 13 – 16 and 21 – 23 of the Lochhead Declaration submitted in connection with October 9, 2007 Response to Non-Final Office Action. In Paragraph 13, Dr. Lochhead explains that partition coefficient is determined, in large part, based on solubility. He then relates partition coefficient to lipophilicity and explains how a person having ordinary skill in the art would understand these concepts based on the disclosures of the Embil/Nacht Appln – including, in particular, Paragraph [0068] as follows: lipophilicity, according to the Embil/Nacht Appln means the partition coefficient of an active ingredient in a Microsponge (or other polymeric delivery system) versus the partition coefficient of the active ingredient in the carrier base in which the Microsponge is formulated. I read and understand "substantially the same lipophilicity" as that phrase is used in the Embil/Nacht Appln in the same manner as Dr. Lochhead.

11. At Paragraphs 15 and 16 of this Declaration, Dr. Lochhead analyzed the solubility of benzoyl peroxide in different aqueous carriers. Based on the data presented in Table 2 of his Declaration, Dr. Lochhead further analyzed the combination formulations taught in the examples of WO26. (These example combination formulations are made up of two components – a benzoyl peroxide suspension and a clindamycin solution.) The benzoyl peroxide suspensions taught in WO26 Example 5 and WO Example 6 contain, respectively, 11.56 weight % and 7.5 weight % of propylene glycol. The solubility of benzoyl peroxide, and therefore its lipophilicity in a suspension, will be significantly influenced by differences in the amount of propylene glycol. Based on the differences between the two component parts, Dr. Lochhead concludes that these components do not exhibit "substantially the same lipophilicity" as defined in Paragraph

[0068] of the Embil/Nacht Appln. I fully agree with this conclusion.

12. A person having ordinary skill in the art of formulating topical products would understand WO26 as teaching a polymeric gelling agent – specifically, carboxy vinyl polymers. As Dr. Lochhead explained at Paragraphs 8 and 11 of his Declaration, carboxy vinyl polymers would not be understood by a person having ordinary skill in the art to be a "polymeric delivery system" as this term is defined in Paragraph [0050] of the Embil/Nacht Appln.

13. A person having ordinary skill in the art would recognize carboxy vinyl polymers to be viscosity-thickening agents for aqueous or hydric solvent systems and would also understand and recognize that these polymers are not a polymeric delivery system of the type claimed in the Embil/Nacht Appln.

14. In the Response to Office Action filed on October 9, 2007, the Embil/Nacht Appln added claims for a product comprised of two compositions each having viscosities of less than about 40,000 cps (Claim 29), and less than about 30,000 cps (Claim 30). My understanding is that two new claims are being added in the Response to Office Action being filed with this Declaration. These new claims are for a finished topical product having two component compositions, each having viscosities of less than about 20,000 cps (New Claim 31) and less than about 10,000 cps (New Claim 32). Lower, matched viscosities have an important therapeutic benefit – they allow for reproducible administration of a desired dose of active ingredient(s) from a dual-chamber dispenser. In other words, the lower, matched viscosities help assure that each time a consumer or patient actuates the dual chamber pump, thereby dispensing the two component compositions, the resulting finished product contains substantially the same intended dose of active ingredient in each administration.

15. WO26, EP, Katz and Wester do not teach or suggest a finished topical product

comprised of two component compositions, each having viscosities of less than about 20,000 cps or less than about 10,000 cps.

16. In Paragraph 27 of his Declaration, Dr. Lochhead discussed the viscosity of the two component compositions taught in the WO26 reference – benzoyl peroxide as a suspension and clindamycin as solution. According to the disclosure of W026, the viscosity of the benzoyl peroxide component composition (prior to mixing with the clindamycin solution) is from 50,000 - 90,000 cps, preferably from 65,000 – 85,000 cps. WO26 does not teach the viscosity of the example clindamycin solutions. Dr. Lochhead, however, estimated that these compositions would have a viscosity of less than 100 cps. Based on my over 40 years of experience in formulating topical products I agree with Dr. Lochhead's estimation. Instead, WO26 teaches that a gelling agent is added to the benzoyl peroxide suspension. (See WO26, page 6, lines 30 – 32.) In contrast, the clindamycin solution examples in Examples 1 – 4 of WO26 do not contain any ingredient that a person having ordinary skill in the art would understand to be a gelling agent. More particularly, the clindamycin solutions contain preservatives (parabens and imidurea) as well as a buffering agent (potassium hydroxide). These ingredients at the indicated use levels would not impart any meaningful increase in viscosity, certainly no where on the same order of magnitude of 50,000 to 90,000 cps which is taught for the combined benzoyl peroxide suspension. Thus, WO26 does not teach two compositions having substantially the same viscosity. Nor does WO26 teach compositions having viscosities in the ranges claimed by Drs. Embil and Nacht (i.e., less than about 20,000 cps and less than about 10,000 cps).

17. Reproducibility is also desirable for another equally if not more important reason – safety. Based on my experience, not only as a formulator of topical products, but also

as a consultant to topical pharmaceutical companies including Medicis (a pharmaceutical company focusing primarily on the treatment of dermatological conditions including acne, fungal infections, psoriasis, rosacea and seborrheic dermatitis), Dow Pharmaceutical Sciences (a company founded by the co-inventor of WO26) as well as Psoriasis Research Institute, it is my understanding that practicing dermatologists give a patient prescriptions on the average for two or three different products. If two products are to be applied at the same time, as is common, the mixing of different base formulations could result in unintended dose dumping. In the case of many therapeutically-active ingredients – including, for example, retinoids and corticosteroids – applying too large a dose too quickly can result in irritation as well as other negative sequelae, including thinning of the skin. The Embil/Nacht Appln addresses this issue by creating a system in which a therapeutically-active is entrapped in a reservoir within a polymeric delivery system in a single formulation and released in smaller doses at a steady rate over a longer period of time in a combination formulation.

18. In addition, the mixing of different base formulations can also cause incompatibilities that can result in undesirable precipitation, crystallization or separation of the active ingredients and/or vehicle components. Matching lipophilicity and viscosity in the manner claimed by Drs. Embil and Nacht mitigates this potential.

Further Declarant says not.

Dated: June 26, 2008
Menlo Park, California

Martin Katz, Sc.D.